Breast cancer: complete response with the combination of sunitinib and trastuzumab in a patient with grade III ductal carcinoma

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In August 2000, a previously healthy postmenopausal 52-year-old woman was diagnosed with grade III invasive ductal carcinoma. The tumor had an ER -, PR -, and HER2 + profile. Adjuvant treatment with FEC was initiated followed by radiotherapy. In October 2004, the patient presented a clinically asymptomatic supraclavicular and mediastinal lymph node recurrence and treatment with paclitaxel and trastuzumab was initiated. A complete response was achieved after 20 weeks of treatment, and in January 2006 treatment was interrupted due to toxicity. After a 34-month free-of-relapse period, a local recurrence was detected in the chest wall. In September 2007, the patient joined a phase II trial with sunitinib (37.5 mg once a day in 28 days cycles) and trastuzumab (6 mg/kg every 3 weeks), after having verified a normal cardiac function. After two courses, a partial cutaneous response and a complete radiological response were obtained. The most relevant toxicities included cutaneous hyperpigmentation, dysgeusia, mucositis, grade II diarrhea and hypertension. The development of grade III diarrhea led to sunitinib dose reduction (25mg/day). In January 2008, the patient developed hypotiroidism and a significant drop in the left ventricular ejection fraction that led to treatment interruption. In March 2008, once cardiac function was recovered, treatment at the same dose was reinitiated. After two months of treatment, a new descent in cardiac function was noted which led to the suspension of sunitinib, and the interruption of the trastuzumab treatment until recovery of normal cardiac function. In July 2008, trastuzumab monotherapy was resumed and since then no cardiac events have been reported, while maintaining a radiological and clinical response.
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Case report

A previously healthy postmenopausal 52-year-old woman presented in August 2000 with a suspicious group of microcalcifications in the left upper portion of the breast in a screening mammogram. An ultrasound-guided core needle biopsy was performed providing an invasive breast cancer diagnosis. The patient underwent a modified radical mastectomy and ipsilateral axillary lymph node dissection that showed an invasive ductal carcinoma of 2.5 cm, grade III, with metastasis in 11 out of the 21 resected axillary lymph nodes. The specimen had a negative hormone receptor (estrogen and progesterone) and a positive her2/neu (+ + + / + + +) profile by IHC. She received adjuvant treatment with chemotherapy based on an anthracycline-containing FEC combination [5-fluorouracil (5-FU) 600 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 every 21 days] for six cycles. Afterwards, radiation therapy was delivered on the right chest wall, supraclavicular fossa, and axilla at a total dose of 50 Gy.

In October 2004, she presented a clinically asymptomatic supraclavicular and mediastinal lymph node recurrence and treatment was initiated with a weekly paclitaxel (80mg/m^2) plus trastuzumab (2 mg/kg) regimen. A complete response was obtained after 20 weeks of treatment, and in January 2006 the treatment was interrupted because of neurotoxicity.

After a 34-month free-of-relapse period, in August 2007, local recurrence in the chest wall was detected. A computed tomography scan showed a 3 cm lung node and axillary disease (Fig. 1) [1,2].

The her2/neu status was confirmed by fluorescence in-situ hybridization in the primary tumor specimen. She was offered to participate in a phase II trial with sunitinib 37.5 mg once a day in 28 day cycles plus trastuzumab 6 mg/kg every 3 weeks. After verifying a normal cardiac function with an echocardiogram [left ventricular ejection fraction (LVEF) of 68%], treatment was initiated in September 2007. After two courses of chemotherapy, a partial cutaneous response and a complete radiological response were obtained (Fig. 2). Cutaneous hyperpigmentation, dysgeusia, mucositis, grade II diarrhea, and hypertension that needed hydrochlorothiazide to achieve a good

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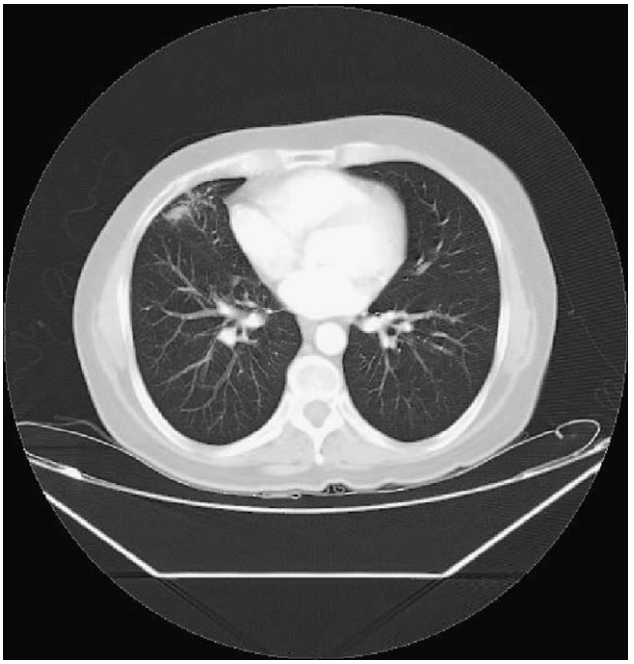
control were the most relevant toxicities. On account of the presence of grade III fatigue, the dose of sunitinib had to be reduced to 25 mg/day, improving the side-effects control after the dose adjustment and allowing the treatment maintenance according to the study protocol.

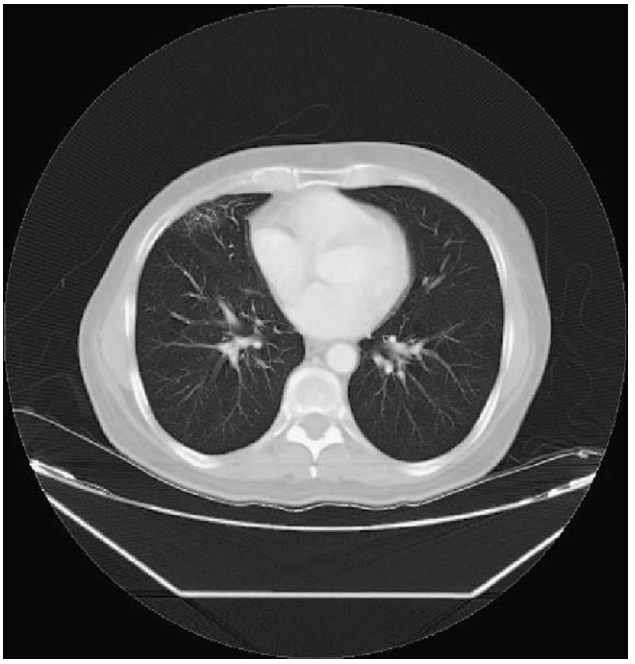
In January 2008, laboratory tests showed hypothyroidism and levothyroxine 25 µg per day was prescribed. At the same time, electrocardiographic changes (ST-segment depression and T-wave inversion (Fig. 3) and a significant drop in the LVEF (40%) was observed, therefore

Fig. 1



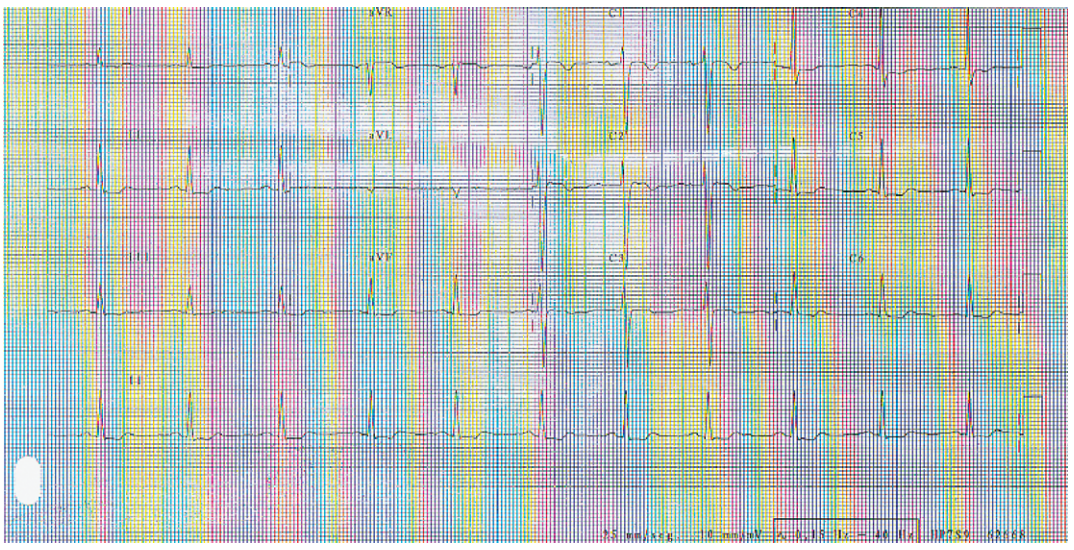
Computed tomography scan: lung node metastasis at the beginning of the treatment with sunitinib plus trastuzumab in the phase II clinical trial (August 2007).

Fig. 2



Computed tomography scan: almost complete disappearance of lung node metastasis after 3 months of treatment with sunitinib plus trastuzumab (November 2007).

Fig. 3



Electrocardiographic changes after sunitinib treatment: ST-segment depression and T-wave inversion (January 2008).

chemotherapy treatment had to be interrupted. The patient referred orthopnea and mild malleolar edemas as her only clinical symptoms. In March 2008, once the cardiac function was recovered, treatment at the same dose was reinitiated. However, a new descent in the cardiac function measured by echocardiogram (< 40%) was detected after 2 months of treatment, and subsequently sunitinib was definitely suspended while trastuzumab was only interrupted until the cardiac function returned to normal values. Then, in July 2008 monotherapy with trastuzumab was resumed and since then no cardiac events have been reported so far while a maintained radiological and clinical response has been observed.

Discussion

The growing body knowledge gained in the last few years regarding the breast cancer biology, more specifically about angiogenic mechanisms and other signalling pathways involved in cancer progression and metastasis, has promoted the development of new molecules. Sunitinib is an orally administered small molecule agent that inhibits the tyrosine kinase enzimatic activities of the vascular endothelial growth factor and platelet-derived growth factor receptors, and also blocks the Kit, FLT3, and RET signalling pathways, thereby inhibiting angiogenesis and cell proliferation. It is indicated for the treatment of imatinib-resistant gastrointestinal stromal tumors [3] and for renal cell carcinoma [4]. A single, multitargeted agent has several potential advantages such as less toxicity, simplified dosing, and way of administration, and it can potentially be combined with other treatments. These are the reasons supporting the design of different phase II and III trials currently ongoing in different types of tumors, as in the case of breast cancer.

Preclinical data show that sunitinib has cytoreductive antitumor activity in breast cancer, enhances the activity of chemotherapy, and inhibits osteolytic tumor progression in breast cancer bone metastasis [2,5]. In fact, sunitinib malate has also been tested in combination with docetaxel, doxorubicin, and 5-FU in a MX-1 human breast cancer xenograft model. The antitumor activity of the three antineoplastic agents was enhanced by sunitinib malate and the effect was accompanied by a significant increase in survival. Single-agent sunitinib therapy has shown clinically relevant activity in a phase II clinical trial enrolling patients with previously treated metastatic breast cancer. Sunitinib was given at the dose of 50 mg per day for 4 weeks followed by 2 weeks off treatment in monotherapy and the endpoint was objective response rates based on Response Evaluation Criteria In Solid Tumors criteria. Patients should have received prior anthracycline and taxane therapy (either in the adjuvant and/or in the metastatic setting) to be included, and they could be either estrogen receptor and her2/neu status negative or positive (31% were triple negative). Sixty-three patients were randomized and an 11% rate of partial responses and up to a 19% rate of clinical benefit were observed [1]. Among those patients experiencing partial response, three had her2/neu-positive disease and had previously received trastuzumab in the advanced setting, and three had triple-negative disease according to their estrogen receptor, progesterone receptor, and her2/neu status. There are other phase II and III ongoing trials that are aiming to study the combination of sunitinib with chemotherapy (paclitaxel, capecitabine, or docetaxel) in advanced breast cancer that will provide results within the next coming years.

However, based on the observation that superficial/palpable or visible/ or clinically evaluable lesions may start to regrow during the 2-week rest period of sunitinib when dosed intermittently, it can be hypothesized that continuous schedules of sunitinib at lower doses and without treatment breaks might result in an improved efficacy, while maintaining good tolerability. Thus, it has been suggested that a continuous dose regimen deserves further evaluation in the context of clinical trials [6].

The main relevant adverse reactions described with the use of sunitinib are gastrointestinal symptoms such as diarrhea, nausea, dysgeusia and mucositis; cutaneous hyperpigmentation and handfoot syndrome; leukopenia, anemia and thrombocytopenia (generally grades I/II), metabolic disorders such as hypotiroidism and fatigue, and cardiovascular events. Among the different cardiovascular toxicities, the most frequent is hypertension that is usually well controlled with hypotensors (with regular antihypertensive drugs). A decrease in the LVEF has been reported in 11–20% (1% of grades III/IV), hence a close monitoring with a basal and periodical echocardiographic evaluations are mandatory for sunitinib-treated patients [7].

In the present case, both trastuzumab and sunitinib are known to have cardiac toxicity. During the monitorization of the cardiac function two episodes of LVEF olygosymptomatic decrease were detected. This cardiac toxicity disappeared when treatment with both drugs was interrupted. It cannot be concluded whether this event was exclusively related with the administration of sunitinib or with the combination of the two drugs. The patient was also diagnosed during the treatment of asymptomatic hypothyroidism that was properly controlled with levothyroxine. Despite the interruptions in the treatment because of toxicity, the patient achieved a complete response with the combination.

Only the results of the ongoing clinical trials will allow us to know the best way to combine these new groups of molecular-targeted therapies and to understand their real benefits in the clinical practice.

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